Vascular Medicine

The Challenge of Diagnosing Atheroembolic Renal Disease
Clinical Features and Prognostic Factors

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Background—Atheroembolic renal disease (AERD) is caused by showers of cholesterol crystals released by eroded atherosclerotic plaques. Embolization may occur spontaneously or after angiographic/surgical procedures. We sought to determine clinical features and prognostic factors of AERD.

Methods and Results—Incident cases of AERD were enrolled at multiple sites and followed up from diagnosis until dialysis and death. Diagnosis was based on clinical suspicion, confirmed by histology or ophthalmoscopy for all spontaneous forms and for most iatrogenic cases. Cox regression was used to model time to dialysis and death as a function of baseline characteristics, AERD presentation (acute/subacute versus chronic renal function decline), and extrarenal manifestations. Three hundred fifty-four subjects were followed up for an average of 2 years. They tended to be male (83%) and elderly (60% >70 years) and to have cardiovascular diseases (90%) and abnormal renal function at baseline (83%). AERD occurred spontaneously in 23.5% of the cases. During the study, 116 patients required dialysis, and 102 died. Baseline comorbidities, ie, reduced renal function, presence of diabetes, history of heart failure, acute/subacute presentation, and gastrointestinal tract involvement, were significant predictors of event occurrence. The risk of dialysis and death was 50% lower among those receiving statins.

Conclusions—Clinical features of AERD are identifiable. These make diagnosis possible in most cases. Prognosis is influenced by disease type and severity. (***Circulation***. 2007;116:298-304.)

Key Words: anticoagulants ■ atherosclerosis ■ catheterization ■ cholesterol ■ diabetes mellitus
■ fibrillation ■ peripheral vascular disease

Atheroembolic renal disease (AERD) is part of a multi-systemic disease caused by occlusion of small arteries by cholesterol crystal emboli deriving from ulcerated atherosclerotic plaques.[1–6] Lesions distal to cleft lodgment are both ischemic and inflammatory, depending on the extent of embolization.[6] Indeed, the release of cholesterol emboli into the circulation may occur repeatedly in a spontaneous fashion or after vascular trauma with angiographic catheters, vascular surgery, or use of anticoagulants and thrombolytic agents.[4,6] Because the aorta is the most common source of crystals, the kidney, intestine, and legs are at prime risk of embolization.

AERD is an important yet underdiagnosed component of the spectrum of kidney diseases associated with atherosclerosis and remains an unexplored field of nephrology research. In the last decades, the disorder evolved slowly from a pathological curiosity to a clinical entity.[6] AERD was fre-

quently overlooked as a cause of renal dysfunction during life, with the diagnosis often being made postmortem.[1,7] Although recent clinical studies have improved our understanding of AERD, its diagnosis remains challenging because more organs can be affected, mimicking a variety of disorders.[4,6,8] Indeed, as stated in a recent clinical problem-solving article, making a correct diagnosis of AERD has been considered similar to finding "a needle in the haystack."[9]

The present study illustrates the main clinical manifestations and follow-up data of a large group of patients referred to the nephrologist for renal function decline and in whom AERD was diagnosed. We believe that the knowledge of these features can help physicians to make a correct diagnosis of AERD in most cases and estimate its prognosis.[6,7]

Methods

Study Design and Inception Cohort Assembly

The present study cohort includes 354 incident cases of AERD recruited at 12 tertiary care centers in 3 main areas of northern Italy between June 1987 and January 2006 (Lombardy-Emilia-Piemonte). Data collection was retrospective for 35 cases identified by January 1995.[5–7] Subsequently, a multisite prospective study was planned and approved by the local ethical review committees.[8] Preliminary data on 95 subjects from a single center have been reported previously.[8]

Referral Patterns and Diagnosis

Patients were identified on referral to a nephrologist because of concern about kidney function, and the initial consideration of AERD was based on clinical features. Diagnosis was confirmed in all spontaneous forms and in the majority of iatrogenic cases by histology or diagnostic ophthalmoscopic findings. Per protocol, diagnosis of iatrogenic AERD was made in the presence of the following: (1) renal function deterioration occurring in atherosclerotic patients; (2) simultaneous ischemic changes to the lower abdomen and/or extremities; and (3) presence of 1 or more precipitating factors, including arterial angiography with or without angioplasty, vascular abdominal or cardiac surgery, and fibrinolytic or anticoagulant therapy (heparin or oral vitamin K antagonists) usually administered for acute myocardial infarction or atrial fibrillation. In this setting, the diagnosis of AERD was made also in the absence of histological confirmation or retinal emboli. The spontaneous form of AERD was diagnosed only when, following clinical suspicion, a skin, gastrointestinal, or renal biopsy documented cholesterol clefts or, alternatively, when the funduscopic examination disclosed retinal emboli. Signs of extrarenal involvement, eosinophil count, and the rate of renal function deterioration were considered to evaluate the severity of the disease.

Data Collection

Demographic, clinical, and pathological data as well as exposure to precipitating maneuvers were recorded at the time of AERD diagnosis. Serum creatinine concentration was available shortly before the precipitating event for iatrogenic forms and in the year before the onset of symptoms for spontaneous forms. Information on renal function was updated at the time of AERD diagnosis and during the course of the acute or subacute phase of renal disease and was reassessed at each follow-up visit for those with milder forms.

Follow-Up Information

Cases were followed up from diagnosis until end-stage renal disease (ESRD) and death. Trends in case characteristics and event rates among those enrolled at various periods were sought. To minimize loss to follow-up, patients were contacted by telephone within 2 months of the study end date (June 2006) if they were not known to be already on dialysis or dead. For out-of-hospital deaths, family members were interviewed to ascertain the circumstances surrounding the death.

Renal Failure

Renal function was estimated with the use of the abbreviated Modification of Diet in Renal Disease formula.[10] Categories were defined as chronic kidney disease absent/mild: glomerular filtration rate (GFR) >60 mL/min (1 mL/s, stage 1 to 2); moderate: GFR 60 to 30 mL/min (1 to 0.5 mL/s, stage 3); and severe/advanced: GFR <30 mL/min (0.5 mL/s, stage 4 to 5).[11] With respect to the clinical presentation of AERD, renal failure was defined as acute if a sudden 50% reduction of GFR was evident within 1 week after the precipitating event; subacute if the same deterioration occurred in a stepwise fashion over 2 to 6 weeks; and chronic if the patient had a stable chronic renal impairment mimicking nephroangiosclerosis.

Comorbid Conditions and Cardiovascular Risk Factors

The following were considered vascular comorbidities: coronary artery disease (evidence of angina or previous myocardial infarction); cerebrovascular disease (clinical signs or radiological confirmation of a transient ischemic attack or cerebrovascular accident); peripheral vascular disease (symptoms of intermittent claudication, previous surgery for lower-limb arterial insufficiency, and/or angiographic evidence of significant stenosis in 1 or more blood vessels supplying the lower limbs). The diagnosis of congestive heart failure was based on symptoms of pump failure (New York Heart Association classification class II or greater). Angiography or magnetic resonance angiography was used to confirm abdominal aortic aneurysm or renal artery stenosis (>50% in 1 or both renal arteries) when these lesions were suspected. Patients were considered diabetic if they had been given either oral antidiabetic drugs or insulin and were considered smokers in case of either current or previous smoking habit (at least 10 cigarettes per day and for >10 years). Hypercholesterolemia was defined by total cholesterol levels >220 mg/dL or if cholesterol-lowering treatment was prescribed. Hypertension was defined as systolic or diastolic pressure of >140 mm Hg or >90 mm Hg, respectively, or if antihypertensive drugs had been given.

Statistical Analyses

Baseline Characteristics and Univariate Comparisons

Quantitative and qualitative variables were compared with the use of t test, χ^2 test, or exact test, as appropriate. Because of the high number of statistical tests, a 2-tailed probability value <0.01 was considered significant in this crude comparison of the form of AERD.

Outcome Procedure

Times from diagnosis to ESRD (defined as need for dialysis therapy) and death or censoring (last follow-up visit) were described with the Kaplan-Meier method. Cox regression was used for multivariate analysis. Because both dialysis and death could occur in the same patient, a competing risk model for double unordered failure events of different types was fitted.[12] In these cases, the event times are correlated within individuals, and this violates the independence assumption required by standard techniques. The lack of independence of the failure times was accounted for by incorporating the individual frailty (random effect) into the model.[13] Consistency of the results was checked by running the corresponding variance-corrected (or robust) model.[12] The model was stratified by event type and center area. The contribution of the covariates to explain the dependent variable was assessed by means of a 2-tailed Wald test, with $P<0.05$ considered significant. Model specification and overall fit were checked by reestimation, formal and graphical tests based on residuals, and testing the interaction with time of the variables in the model.[13]

Model Building

A manual selection approach was used, screening for multicollinearity and interactions and considering first a baseline model of (1) variables present before zero time: baseline characteristics, traditional cardiovascular risk factors, and comorbidity; then (2) factors acting closer to the onset of the AERD, ie, precipitating factors; (3) markers of clinical severity of the AERD: time course of kidney function deterioration (acute/subacute renal failure versus chronic), involvement of extrarenal organ systems (legs, gastrointestinal tract, and central nervous system); and finally (4) incorporating treatments initiated after diagnosis: pentoxifylline, statins, and steroids. Covariates were retained in the model if their effects were significant at the 0.1 level or modified the parameter estimates of other significant predictors. Calculations were made with the use of R.[14]

Results

Baseline Characteristics, Risk Factors, and Clinical Findings

Demographic and clinical characteristics of the 354 patients are summarized in Tables 1 and 2. Patients tended to be male

TABLE 1.   Baseline Patient Characteristics and Risk Factors*

	All (n=354)	Iatrogenic (n=271)	Spontaneous (n=83)	P†
Age, y	71.1±7.8	70.6±7.4	72.6±7.6	0.040
Male gender	295 (83.3)	228 (84.1)	67 (80.7)	0.466
No history of hypertension	61 (17.2)	49 (18)	12 (14.4)	0.733
Hypertension for ≤10 y	121 (34.1)	91 (33.5)	30 (36.1)	...
Hypertension for >10 y	172 (48.6)	121 (48.3)	41 (49.4)	...
Smoking habit	246 (69.5)	194 (71.6)	52 (62.6)	0.122
Diabetes	64 (18)	48 (17.7)	16 (19.2)	0.746
Hypercholesterolemia	123 (34.7)	91 (33.5)	32 (38.5)	0.405
Statin use	104 (29.3)	84 (31)	20 (24.1)	0.227
Coronary artery disease	218 (61.5)	193 (71.2)	25 (30.1)	<0.001
Peripheral artery disease	205 (58)	153 (56.4)	52 (62.6)	0.317
Cerebrovascular disease	120 (33.9)	87 (32.1)	33 (39.7)	0.197
Heart failure	105 (29.6)	84 (31)	21 (25.3)	0.320
Cardiovascular disease	320 (90.4)	253 (93.3)	67 (80.7)	0.001
GFR‡	42±18	44.2±18.2	38±16.7	0.004
CKD§ stages 1–2	62 (17.5)	51 (18.2)	11 (13.2)	0.012
CKD stage 3	196 (55.3)	157 (57.9)	39 (47)	...
CKD stages 4–5	96 (27.1)	63 (23.2)	33 (40)	...
Renal artery stenosis‖	59 (34)	52 (35)	7 (28)	0.500

*Values are expressed as mean±SD or n (%) as appropriate.

†P: 2-sided significant level (χ^2/exact).

‡GFR in mL/min per 1.73 m².

§CKD stages 1–2 (GFR >60), stage 3 (GFR 30–60), stages 4–5 (GFR <30).

‖Data available in 174 subjects.

and aged >70 years (60%), with high prevalence of traditional cardiovascular risk factors and cardiovascular diseases. Average (SD) total cholesterol level was 204.6 (51) mg/dL, and the estimated GFR at baseline was 42 mL/min per 1.73 m². Interestingly, only 17.5% of the patients had chronic kidney disease stage 1 to 2. Urinalysis showed bland urine with minimal proteinuria. However, 15 patients with histologically confirmed AERD and long-standing type 2 diabetes had >1 g/d proteinuria. The legs represented the most common extrarenal site involved. The majority of patients had an iatrogenic form of AERD, with coronary angiography via the femoral artery the most common precipitating factor.

Acute/subacute onset was more likely in iatrogenic than spontaneous forms (93.3% versus 31.3%; P<0.001). Histological or ophthalmoscopic confirmation was available for all spontaneous cases and 51.3% of iatrogenic cases. In 20 subjects, the diagnosis was confirmed only by the finding of retinal emboli. The manner in which the diagnosis was confirmed and the distribution of case characteristics did not change over the study period, with the exception of an increased utilization of statins in the last 6 years (from 20% to 30% to 50%).

Renal Outcome

The average (SD) GFR values at onset and at the time of peak serum creatinine were 22.9 (13.2) mL/min per 1.73 m² and 12.2 (8.4) mL/min per 1.73 m², respectively. One hundred sixteen patients (32.7%) required dialysis therapy (Figure 1a), with the risk being especially high within 6 months of the

event. The treatment modality for the majority of the patients was hemodialysis (89 patients). Eighty-three patients remained on maintenance dialysis therapy, and 33 recovered sufficient renal function to stop dialysis (GFR levels 17±4 mL/min per 1.73 m²). However, 5 of those patients restarted dialysis by the end of the study (within 2 to 6 months of stopping therapy). Cumulative renal survival probability was reduced by the presence of heart failure (P<0.001), baseline chronic kidney disease categories (P<0.001), age >70 years (P=0.039), iatrogenic form (P<0.001), acute/subacute modality onset (P<0.001), and leg (P=0.007) or gastrointestinal involvement (P<0.001). Statin treatment was associated with protective effects both when already in place at the time of diagnosis and when initiated after diagnosis (P<0.001). At multivariable analysis, the same factors plus diabetes were associated with a significant increased risk for ESRD (Figure 2).

Patient Survival

The mean follow-up of the cohort as a whole was 24 months, with a median survival of 66 months and 730 patient-years at risk (Figure 1b). During the study, 102 patients died. The cause of death was ascertained for 72 patients. Cardiovascular disease was the main cause of mortality, accounting for 58 deaths (80%); 6 patients died from infection and 8 due to other causes (cachexia, ischemic colitis, pancreatitis). At univariable analysis, the same factors affecting renal survival were significant predictors of patient survival. Separate regression of renal and patient outcomes identified the same

TABLE 2.   Clinical Findings*

	All (n=354)	Iatrogenic (n=271)	Spontaneous (n=83)	P†
Precipitating factors				
Angiography	221 (62.4)	221 (81.5)	...	...
Percutaneous angioplasty	90 (25.4)	90 (33.1)	...	...
Cardiovascular surgery	69 (19.5)	69 (25.4)	...	...
Anticoagulant/fibrinolytic therapy	108 (30.5)	108 (39.8)	...	...
1 precipitating factor	122 (45.0)	122 (45)	...	...
2 precipitating factors	86 (31.7)	86 (31.7)	...	...
≥3 precipitating factors	63 (23.3)	63 (23.2)	...	...
Presentation				
Acute renal failure	76 (21.4)	71 (26.2)	5 (6)	<0.001
Subacute renal failure	203 (57.3)	182 (67.1)	21 (25.3)	<0.001
Chronic renal failure	75 (21.2)	18 (6.6)	57 (68.6)	<0.001
Skin manifestations‡	266 (75.1)	223 (82.3)	43 (51.8)	<0.001
Central nervous system§	35 (9.8)	27 (9.9)	8 (9.6)	0.931
Gastrointestinal involvement‖	43 (12.1)	38 (14)	5 (6)	0.051
Eosinophil count >500 cells/μL	238 (67.2)	194 (71.6)	44 (53)	0.002
Diagnosis and confirmation				
Clinical only	132 (37.3)	132 (48.7)	...	...
Plus skin biopsy	133 (37.5)	98 (36.1)	35 (42.1)	0.323
Plus renal biopsy	63 (30.3)	20 (7.4)	43 (51.8)	<0.001
Plus other biopsy	4 (1.1)	3 (1.1)	1 (1.2)	0.939
Plus nephrectomy	2 (0.5)	1 (0.3)	1 (1.2)	0.374
Plus autopsy	9 (2.5)	6 (2.2)	3 (3.6)	0.478
Plus ophthalmoscopy	24 (6.7)	22 (8.1)	2 (2.4)	0.082
Treatments				
Statins initiated	115 (32.4)	97 (35.8)	18 (21.7)	0.002
Steroids	154 (43.5)	130 (48)	24 (28.9)	0.001
Pentoxifylline	78 (22)	62 (22.9)	16 (19.3)	0.489
Dialysis therapies (n=116)				
Any dialysis therapies vs none	116 (32.7)	101 (37.2)	15 (18)	0.001
Peritoneal dialysis vs hemodialysis therapies	27 (23.2)	21 (20.8)	6 (40)	0.100
Temporary vs permanent dialysis therapies	33 (28.4)	31 (30.7)	2 (13.3)	0.164

*Variable values are expressed as n (%).

†P: Two-sided significant level (χ^2/exact).

‡Purple toes/livedo reticularis on the feet/lower abdomen.

§Transient ischemic attack, amaurosis fugax, confusional states, and gradual deterioration of neurological functions.

‖Abdominal pain, diarrhea, bleeding, intestinal infarction.

predictors that were tested in multiple events analysis (Figure 2).

Both renal and death event rates were similar in successive 3-year study periods. Results did not change when patients enrolled during the retrospective study were excluded. All identified predictors had equivalent prognostic implications for both renal and death events. Robust (variance-corrected) methods yielded the same results.

Discussion

The diagnosis of AERD has challenged physicians for a century.[1–6,15,16] The large size of this cohort and the length of follow-up of our study allow an accurate evaluation of the main characteristics of AERD, including risk factors, precipitating events, clinical and laboratory findings, and renal and patient outcomes. The key findings of our study are 3-fold. First, AERD was seen in 2 forms. The acute/subacute form likely results from a massive shower of emboli or multiple cyclic embolizations due to abrupt or repeated rupture of unstable plaques. Conversely, chronic AERD is likely due to slow release of crystals from eroded atherosclerotic lesions.[6,9] Second, the study emphasizes the growing role of invasive procedures (cardiac catheterization and cardiovascular surgery) and fibrinolysis/anticoagulation as triggering factors. The disease was iatrogenic in the majority of cases, often associated with multiple triggering factors. The most com-
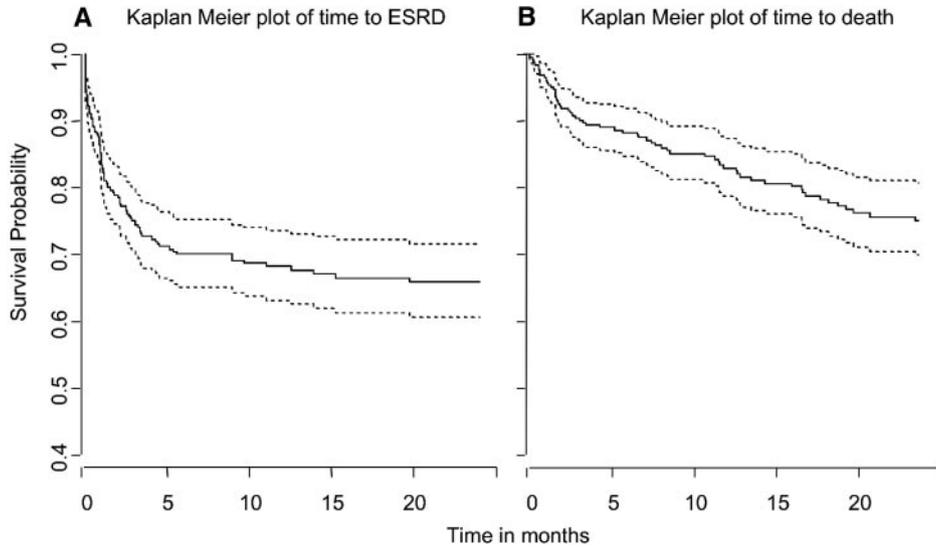
Figure 1. Kaplan-Meier survival curve and 95% CI of time to ESRD (A) and patient death from diagnosis (B).

mon triggering event was coronary angiography via the femoral artery, with mechanical trauma as the proposed mechanism of injury. Catheter manipulations disrupt atherosclerotic aortic plaques, exposing the soft, cholesterol-laden core of the plaque to the arterial circulation. If the introduction of catheterization techniques has greatly improved the diagnosis and treatment of cardiovascular diseases, AERD now may be considered 1 major adverse effect. Interestingly, the second most frequent precipitating factor consisted of anticoagulant (including both heparin and oral anticoagulants) or thrombolytic treatment. These agents may initiate the disruption of complex plaques by causing internal hemorrhage or lysis of intraintimal or cap thrombi. However, few data are available on the possible inciting role of anticoagulation and thrombolytic therapy. The role of these agents may have been strengthened by their widespread use for atrial fibrillation and acute myocardial infarction. A minority of

patients of this cohort suffered from spontaneous detachment of a plaque or low-grade, clinically silent migration of crystals from the aortic wall. Iatrogenic AERD showed worse outcomes than spontaneous AERD, despite the likelihood that a lower diagnostic suspicion would lead to selective identification of more severe cases in the spontaneous form. However, the time course of renal insufficiency (acute/subacute versus chronic) was a more accurate prognostic factor. Third, besides the varying degree and time course of renal function deterioration, in most patients an extrarenal involvement was observed with variable combination of cutaneous, gastrointestinal, and neurological manifestations. Such a systemic disease process poses challenges in differential diagnosis.

In the past, many difficulties were encountered in diagnosing AERD.[1–6] Our data suggest that knowledge of the risk factors, recognition of the multifaceted clinical presentations, and a high index of clinical suspicion, particularly after
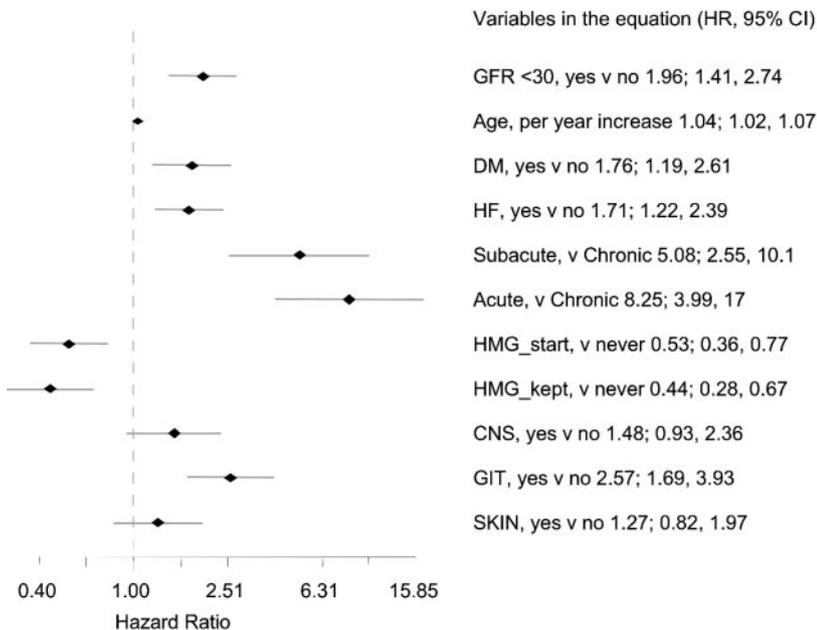

Variables in the equation (HR, 95% CI)

GFR <30, yes v no 1.96; 1.41, 2.74

Age, per year increase 1.04; 1.02, 1.07

DM, yes v no 1.76; 1.19, 2.61

HF, yes v no 1.71; 1.22, 2.39

Subacute, v Chronic 5.08; 2.55, 10.1

Acute, v Chronic 8.25; 3.99, 17

HMG_start, v never 0.53; 0.36, 0.77

HMG_kept, v never 0.44; 0.28, 0.67

CNS, yes v no 1.48; 0.93, 2.36

GIT, yes v no 2.57; 1.69, 3.93

SKIN, yes v no 1.27; 0.82, 1.97

Figure 2. Final frailty Cox model of renal and patient death, stratified by event type and area (n of observations=708 in 354 subjects; 2×3 strata); n of death=102; dialysis starts=116. HR indicates hazard ratio; GFR, glomerular filtration rate at baseline ≤30 mL/min per 1.73 m² (vs greater); age, effect associated with each year of age; DM, diabetes mellitus (present vs absent); HF, heart failure (present vs absent); subacute and acute, disease onset; HMG_start, statins initiated (vs never used); HMG_kept, statins at baseline and maintained (vs never used); CNS, central nervous system involvement (present vs absent); GIT, gastrointestinal tract involvement (present vs absent); and SKIN, involvement of legs (present vs absent).

exposure to triggering events, may permit a correct premortem diagnosis of the disease. The typical patient at risk is a man older than 60 years, with a history of hypertension, smoking, and arterial disease. In such a patient, the triad of a precipitating event, acute/subacute renal failure, and signs of peripheral emboli strongly suggests the diagnosis. In the presence of this triad, the diagnosis of AERD can be made without histology.[1–6] The presence of gastrointestinal bleeding and neurological involvement or eosinophilia should raise the level of suspicion.

Traditionally, renal biopsy has been considered the definitive method for diagnosis of AERD.[1–3,6] However, given the frequency of skin involvement, our study suggests that biopsy of a skin lesion may be a useful, less invasive way of confirming the diagnosis. Alternatively, histological confirmation can be obtained from endoscopic biopsy of gastrointestinal tissues, a less common target organ system. A funduscopic examination provided the opportunity to observe retinal emboli in a subset of patients. Like histology, this procedure may confirm the diagnosis and should never be omitted. It follows that renal biopsy can be avoided in many patients. However, renal biopsy was crucial to the diagnosis of 50% of cases with spontaneous smoldering AERD, which usually mimics nephroangiosclerosis.[17]

AERD has been associated with poor renal and patient survival.[1–6] By the end of follow-up, >30% of our patients were on dialysis. The 1-year and 2-year patient survival probabilities were 83% and 75%, respectively, lower than after acute myocardial infarction or initiation of maintenance dialysis in general.[18,19] The major cause of death was cardiovascular. Compared with previous reports,[5–8] these multicenter data and the statistical approach chosen to model competing risks were powerful enough to establish independent prognostic associations previously undetected, such as the impacts of gastrointestinal involvement, the form of the disease, and heart failure. The analytical strategy was dictated by background physiopathological and clinical epidemiological knowledge about the potential role of the atheroembolic process in the mechanisms of both renal disease and death. It has been shown that appropriate multiple-failure time analyses (ie, accounting for the correlation within the data)[13] offer more relevant information than time to first occurrence only, particularly when patients under study are at risk for >1 event.[8] Of note, the same predictors, ie, older age, comorbid conditions (presence of diabetes and history of heart failure), baseline renal dysfunction, time course of renal function decline, and extrarenal manifestations, were associated with a significant increased risk for both ESRD and death, compatible with a common underlying mechanism leading to renal and cardiovascular events. The higher risk of ESRD and death associated with an acute/subacute renal presentation was probably related to the severity of the embolization.[1–6] Nonspecific presentation leading to diagnostic delay combined with the severe consequences of ischemic injury may explain the adverse effect of gastrointestinal involvement.

Finally, our study confirms and extends previous suggestions that statins may have a beneficial effect on prognosis of AERD.[8] Statin use was associated with better outcomes even when initiated after AERD diagnosis. It is possible that the lipid-lowering and anti-inflammatory properties of statins contributing to plaque stabilization and regression might be beneficial in AERD, as has been demonstrated in acute coronary syndrome.[20,21] However, given the observational nature of the data, confounding by indication and other biases might explain this association, and any inferences drawn from the study should be considered hypotheses to be tested in experimental trials. Use of other therapeutic agents, including steroids, was not associated with outcome. Another limitation of the present study is related to the manner in which subjects were recruited. In fact, because initial identification of cases for our cohort was based on clinical suspicion, the cohort is likely to overrepresent cases with more severe AERD. Accordingly, the estimates of prognosis should only be applied to future cases identified in similar fashion. Although our cases may well be the "tip of an iceberg," milder chronic cases, both iatrogenic and spontaneous, will remain difficult to recognize, and their prognosis may differ from that of the present cohort. Finally, it is possible that the findings of this study may be expected only in a cohort with similar characteristics and in particular with similar prevalence of iatrogenic and spontaneous forms.

In summary, the present study suggests that AERD has become a recognizable cause of renal disease. An antemortem diagnosis of the disease is possible in a significant proportion of cases as long as the level of diagnostic suspicion is high. Because atherosclerosis is highly prevalent and related diagnostic and interventional procedures are increasingly commonplace, differential diagnosis of renal failure in such patients should include AERD. Although no specific treatment has been proven efficacious, use of statins may be justifiable, and such therapy would be a reasonable choice for future treatment trials.

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CLINICAL PERSPECTIVE

Atheroembolic disease is caused by showers of cholesterol crystal emboli deriving from ulcerated atherosclerotic plaques of the aorta and affecting multiple organ systems. The kidney is commonly involved. Although atheroembolization can occur spontaneously, it is increasingly recognized as an iatrogenic complication of invasive percutaneous vascular procedures, including angiography, peripheral and coronary interventions, and vascular surgery, and after anticoagulant or fibrinolytic therapy. Because atheroembolism is ubiquitous, clinical diagnosis of renal atheroembolic disease may be difficult. A triad composed of a precipitating event, occurrence of acute/subacute renal failure, and signs of peripheral embolization may permit diagnosis in a considerable number of cases. Among the laboratory features, helpful clues include the presence of eosinophilia. Skin biopsy from the lower extremities and funduscopy are simple and noninvasive procedures to consider. Atheroembolic renal disease has a meaningful impact on patient prognosis. Benefits of statin treatment are candidate targets of proper randomized trials.

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The Challenge of Diagnosing Atheroembolic Renal Disease: Clinical Features and Prognostic Factors

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